Supplementary Material

Supplementary Appendix 1. Participating Countries and Collaborating Investigators

Argentina: Rodolfo Andres Ahuad Guerrero, Diego Aizenberg, Andres Alvarisqueta, Ines Bartolacci, Mario Alberto Berli, Anselmo Bordonava, Pedro Calella, Maria Cecilia Cantero, Luis Rodolfo Cartasegna, Gabriela Cecilia Coloma, Victor Commendatore, Jesus Cuadrado, Carlos Alberto Cuneo, Ana Maria Cusumano, Walter Guillermo Douthat, Ricardo Dario Dran, Eduardo Farias, Maria Florencia Fernandez, Hernan Finkelstein, Jose Osvaldo Fretes, Nestor Horacio Garcia, Natalia Garrido, Anibal Gastaldi, Elizabeth Gelersztein, Jorge Archibaldo Glenny, Gustavo Cristian Greloni, Adrian Guinsburg, Sonia Hermida, Luis Isaias Juncos, Maria Isabel Klyver, Florencia Kraft, Paulina Virginia Lanchiotti, Ricardo Alfonso Leon de la Fuente, Nora Marchetta, Silvia Ines Orio, Fabian Orteras, Alejandra Oviedo, Jorge Hector Resk, Lucas Rista, Nelson Rodriguez Papini, Jorgelina Sala, Juan Carlos Santos, Lilia Beatriz Schiavi, Horacio Sessa, Tomas Smith Casabella, Maria Rosa Ulla, Augusto Vallejos, Adriana Alicia Villarino, Virginia Esther Visco, Alfredo Wassermann, Cesar Javier Zaidman; **Australia:** Ngai Wah Cheung, Carolyn Droste, Samantha Hocking, Peak Mann Mah, Kathy Nicolls, David Packham, Joseph Proietto, Anthony Roberts, Simon Roger; **Brazil:** Celso Amodeo, Luiz Alberto Andreotti Turatti, Rachel Bregman, Luis Henrique Canani, Fernanda Cristina Camelo Sanches, Antônio Roberto Chacra, Joao Lindolfo Cunha Borges, Sergio Alberto Cunha Vêncio, Fadlo Fraige Filho, Bruno Geloneze Neto, Marcus Gomes Bastos, Suely Keiko Kohara, Elizete Keitel, Jose Francisco Kerr Saraiva, Hugo Roberto Kurtz Lisboa, Domingos Otavio Lorenzoni d'avila, Fabiana Loss de Carvalho Contieri, Pedro Augusto Macedo de Souza, Renan Magalhaes Montenegro Junior, Claudia Moreira de Brito, Miguel Nasser Hissa, Ângela Regina Nazario Sabbag, Irene de Lourdes Noronha, Daniel

Panarotto, Marcio Antônio Pereira, Tiago Schuch, Sergio Seiji Yamada, Roberto Flavio Silva Pecoits Filho, Roberto Simoes de Almeida, Cassio Slompo Ramos, Joao Soares Felicio, Jean Carlo Tibes Hachmann, Cesar Yoiti Hayashida, Tarissa Beatrice Zanata Petry, Maria Teresa Zanella, Roberto Jorge da Silva Franco, Evandro de Souza Portes; **Bulgaria:** Viktoria Andreeva, Angelina Angelova, Stefan Dimitrov, Veselka Genadieva, Gabriela Genova-Hristova, Kiril Hristozov, Boyan Nonchev, Alexander Shinkov, Rangel Rangelov, Margarita Temelkova, Ekaterina Velichkova; **Canada:** Naresh Aggarwal, Ronnie Aronson, Harpreet Bajaj, David Cherney, James Conway, Serge Cournoyer, Gerald DaRoza, Sacha De Serres, Francois Dube, Ronald Goldenberg, Anil Gupta, Milan Gupta, Sam Henein, Hasnain Khandwala, Lawrence Leiter, Adeera Levin, Francois Madore, Alan McMahon, Norman Muirhead, Vincent Pichette, Remi Rabasa-Lhoret, Andrew Steele, Navdeep Tangri, Ali Torshizi, Vincent Woo; **Chile:** Maria Alicia Fernandez Montenegro, Juan Gonzalo Godoy Jorquera, Marcelo Medina, Victor Saavedra Gajardo, Margarita Vejar; **China:** Nan Chen, Qinkai Chen, Shenlian Gan, Linong Ji, Jiao Sun, Yaozhong Kong, Detian Li, Wenge Li, Xuemei Li, Hongli Lin, Jian Liu, Weiping Lu, Hong Mao, Yan Ren, Weihong Song, Lin Sun, Ping Tu, Guixia Wang, Jinkui Yang, Aiping Yin, Xueqing Yu, Minghui Zhao, Hongguang Zheng; **Colombia:** Jose Luis Accini Mendoza, Edgar Gerardo Arcos Palma, Luis Hernando Garcia Ortiz, Alexander Gonzalez Dorado, Eric Hernandez Triana, Juan Diego Higuera Cobos, Dora Ines Molina de Salazar, Joaquin Rodelo, Monica Alexandra Terront Lozano, Luis Valderrama Cometa, Alex Valenzuela, Ruben Dario Vargas Alonso, Ivan Villegas, Hernan Yupanqui; **Czech Republic:** Dagmar Bartaskova, Lenka Dohnalova, Tomas Drasnar, Roman Gregar, Katarina Halciakova, Richard Kovar, Jiri Lastuvka, Magdalena Mokrejsova, Karel Peterka, Jiri Pumprla, Ivan Rychlik, Frantisek Saudek, Vladimir Tesar, Martin Valis, Pavel Weiner, Stanislav Zemek; **France:** Eric

Alamartine, Sophie Borot, Bertrand Cariou, Bertrand Dussol, Jean-Pierre Fauvel, Samy Hadjadj, Alexandre Klein, Yannic Le Meur, Alfred Penfornis, Ronan Roussel, Philippe Zaoui; **Germany:** Markus Faghih, Grit Faulmann, Hermann Haller, Stephan Maxeiner; **Guatemala:** Ronaldo Arturo Gonzalez Orellana, Juan Pablo Moreira Diaz, Luis Alberto Ramirez Roca, Jose Antonio Sanchez Arenales, Jose Vicente Sanchez Polo, Erick Turcios Juarez; **Hungary:** Gyongyi Csecsei, Botond Csiky, Peter Danos, Laszlo Deak, Mihaly Dudas, Katalin Keltai, Sandor Keresztesi, Krisztian Kiss, Laszlo Konyves, Lajos Major, Margit Mileder, Marta Molnar, Tamas Oroszlan, Ivan Ory, Gyorgy Paragh, Eva Peterfai, Gizella Petro, Robert Takacs, Sandor Vangel, Szilard Vasas, Marianna Zsom; **India:** Oomman Abraham, Bhimavarapu Sudhakar, Dewan Deepak, Dinesh Jain, Dinesh Khullar, Natarajan Gopalakrishnan, Noble Gracious, Alva Hansraj, C.B. Keshavamurthy, Fernando M. Edwin, Sahay Manisha, Narayan Prasad, Jayameena Peringat, Ramesh Chandra Vyasam, Raju Sree Bhushan, Reddy Sreedhar, Melemadathil Sreelatha; **Italy:** Pietro Castellino, Luca Chiovato, Salvatore De Cosmo, Luca De Nicola, Giuseppe Derosa, Alberto Di Carlo, Graziano Di Cianni, Giorigio Fuiano, Stefano Genovese, Carlo Giorda, Fabio Malberti, Marcora Mandreoli, Edorado Mannucci, Emanuela Orsi, Piermarco Piatti, Antonio Pontiroli, Domenico Santoro, Roberto Trevisan, Ivana Zavaroni; **Japan:** Hitoshi Akiyama, Hiromi Aoki, Akimichi Asano, Shizuo Kajiyama, Susumu Kashine, Toshio Kawada, Takamoto Kodera, Hiroshi Kono, Kazunori Koyama, Yasuro Kumeda, Shozo Miyauchi, Kazuyuki Mizuyama, Tetsuji Niiya, Hiroko Oishi, Satoshi Ota, Masahiko Takai, Osamu Tomonaga, Mitsuru Tsujimoto, Takashi Wada, Masakiyo Wakasugi, Yasushi Wakida, Takayuki Watanabe, Masayo Yamada, Kazuhiro Yanagida, Toshihiko Yanase, Wataru Yumita; **Lithuania:** Dalia Kozloviene, Antanas Navickas, Egle Urbanaviciene; **Malaysia:** Rohana Abdul Ghani, Khalid Abdul Kadir, Rafidah Abdullah, Norsiah

Ali, Mohd Daud Che Yusof, Mastura Ismail, Wei Yen Kong, Li Yuan Lee, Kien Chien Lim, Soo Kun Lim, Chek Loong Loh, Anita Bhajan Manocha, Kee Sing Ng, Nik Nur Fatnoon Nik Amad, Vanassa Ratnasingam, Paranthaman Vengadasalam; **Mexico:** Melchor Alpizar Salazar, Juan Baas Cruz, Mario Burgos Soto, Jose Chevaile Ramos, Alfredo Chew Wong, Tonatiu Diaz Escalante, Favio Edmuno Enriquez Sosa, Fernando Flores Lozano, Luis Flota Cervera, Paul Frenk Baron, Cecilia Garcia Ballesteros, Jose Gomez Rangel, Luis Enrique Herrera Jimenez, Sergio Irizar Santana, Fernando Jimenez Flores, Hugo Laviada Molina, Cesar Lopez Tarabay, Rosa Luna Ceballos, Belia Martin del Campo, Guadalupe Morales Franco, Oscar Tarsicio Moreno Loza, Cynthia Mustieles Rocha, Gregorio Obrador Vera, Ricardo Orozco Castellanos, Juan Peralta Calcaneo, Miguel Angel Reyes Rosano, Juan Rosas Guzman, Isabel Rucker Joerg, Sandra Saavedra-Sanchez, Jose Hector Sanchez Mijangos, Pablo Serrano Sanson, Juan Tamayo y Orozco, Eloisa Tellez Chavez, Alejandro Valdes Cepeda, Luis Venegas Carrillo, Juan Villagordoa Mesa, Rolando Zamarripa Escobedo; **New Zealand:** John Baker, Russell Scott, Robert Walker, Edward Watson, Michael Williams, Simon Young; **Philippines:** Zaynab Abejuela, Grace Aquitania, Rhea Severina Comia, Olivert Gomez, Florence Santos, Gerry Tan, Marsha Tolentino, Christy Yao, Yvette Ethel Yap, Ma. Dovie Lallaine Ygpuara; **Poland:** Andrzej Januszewicz, Anna Kaminska, Andrzej Madej, Stanislaw Mazur, Dorota Mlodawska-Choluj, Michal Nowicki, Grazyna Orlowska-Kowalik, Grazyna Popenda, Barbara Rewerska, Dariusz Sowinski; **Romania:** Liliana Monica Angelescu, Veronica Anghel, Rodica-Ioana Avram, Mihaela-Magdalena Busegeanu, Adriana Cif, Dana Cosma, Carmen Crisan, Ioana Emilia Ferariu, Ildiko Halmagyi, Nicolae Hancu, Mircea Munteanu, Doru Negru, Ligia Petrica, Amorin Remus Popa, Aurelian-Emil Ranetti, Cristian Serafinceanu; **Russia:** Alina Agafyina, Olga Barbarash, Olga Barysheva, Danila Chizhov, Vladimir Dobronaravov,

Alexander Dreval, Irina Glinkina, Elena Grineva, Elena Kolmakova, Liudmila Kvitkova, Viacheslav Marasaev, Ashot Mkrtumyan, Galina Nagibovich, Sergei Nedogoda, Tatiana Raskina, Yulia Samoylova, Olga Sazonova, Minara Shamkhalova, Elena Shutemova, Tatiana Zykova; **Serbia:** Slobodan Antic, Miodrag Djordjevic, Aleksandra Kendereski, Katarina Lalic, Nebojsa Lalic, Vesna Popovic-Radinovic; **Slovakia:** Jana Baikova, Olga Benusova, Ingrid Buganova, Andrej Dzupina, Peter Fulop, Adriana Ilavska, Emil Martinka, Zuzana Ochodnicka, Daniel Pella, Iveta Smatanova; **South Africa:** Fayzal Ahmed, Aysha Badat, Lawrence Distiller, Vimladhevi Govender, Mukesh Joshi, Jaco Jurgens, Landman Lombard, Mohamed Mookadam, Normangesi Ngcakani, Hendrik Nortje, Helena Oosthuizen, Hans Prozesky, Jeevren Reddy, Mary Seeber; **South Korea:** Dong-Wan Chae, Young Min Cho, In-Kyung Jeong, Sin Gon Kim, Yeong Hoon Kim, Hyuk-Sang Kwon, Min Jeong Kwon, Byung-Wan Lee, JungEun Lee, Moon-Kyu Lee, Moon-Suk Nam, Kook-Hwan Oh, Cheol-Young Park, Sun-Hee Park, Kun Ho Yoon; **Spain:** Pere Alvarez Garcia, Fernando Cereto Castro, Secundino Cigarran Guldris, Marta Dominguez Lopez, Jesus Egido de los Rios, Gema Fernandez Fresnedo, Antonio Galan Serrano, Isabel Garcia, Francisco Javier Gonzalez Martinez, Jose Esteban Jodar Gimeno, Manuel Lopez Mendoza, Tamara Malek Marin, Cristobal Morales Portillo, Maria Antonia Munar Vila, Manuel Munoz Torres, Javier Nieto Iglesias, Jonay Pantoja Perez, Merce Perez Vera, Jose María Portoles Perez, Maria Angustias Quesada Simon, Rafael Simo Canonge, Maria Jose Soler Romeo, Alfonso Soto Gonzalez, Manel Terns Riera, Francisco Jose Tinahones Madueno, Mercedes Velo; **Taiwan:** Chwen-Tzuei Chang, Lee-Ming Chuang, Yi-Jen Hung, Shang-Jyh Hwang, Yung-Chuan Lu, Chih-Ching Lin, Dee Pei, Wayne H.-H. Sheu; **Ukraine:** Olga Barna, Volodymyr Botsyurko, Iryna Dudar, Ivan Fushtey, Olga Godlevska, Oleksandr Golovchenko, Olga Gyrina, Mykola Kolesnyk, Iuliia Komisarenko, Oleksii Korzh,

Nonna Kravchun, Oleg Legun, Borys Mankovskyy, Liliya Martynyuk, Yuriy Mostovoy, Natalia Parshkovska, Larysa Pererva, Tetyana Pertseva, Oleksandr Samoylov, Ivan Smirnov, Yevgeniya Svyshchenko, Galina Tomaskevich, Ivan Topchii, Nadiya Tryshchuk, Vira Tselyuko, Vadym Vizir, Maryna Vlasenko, Tetiana Zlova; **United Arab Emirates:** Salah Abusnana; **United Kingdom:** Paul Ainsworth, Zishan Ali, Vijayaraman Arutchelvam, Maria Barnard, Srikanth Bellary, Emyr Davies, Mark Davies, Simon Davies, Alison Dawson, Mohsen El Kossi, Patrick English, Donald Fraser, Anthony Gunstone, Timothy Hall, Wasim Hanif, Alan Jackson, Andrew Johnson, Franklin Joseph, Singhan Krishnan, Mick Kumwenda, Iain MacDougall, Sam Philip, Shenaz Ramtoola, Manish Saxena, Godwin Simon, Baldev Singh, Jeffrey Stephens, Anna Strzelecka, Rehan Symonds, Wayne Turner, Mona Wahba, John Wakeling, David Wheeler, Peter Winocour; **United States:** Joseph Abdallah, Raied Abdullah, Matthew Abramowitz, Idalia Acosta, Joseph Aiello, Laura Akright, Ayim Akyea-Djamson, Amer Al-Karadsheh, Rajendran Alappan, Radica Alicic, Carlos Arauz-Pacheco, Esperanza Arce-Nunez, Shahabul Arfeen, Ahmed Arif, Naveen Atray, Ahmed Awad, George Bakris, Elizabeth Barranco, Carlos Barrera, Venkata Behara, Diogo Belo, Rhonda Bentley-Lewis, Ramon Berenguer, Marializa Bernardo, Mihaela Biscoveanu, Cynthia Bowman-Stroud, Donald Brandon, Osvaldo Brusco, Robert Busch, Yamil Canaan, Cynthia Christiano, Elena Christofides, Caroucel Cuateco, Kenneth Cohen, Robert Cohen, Charles Cook, Daniel Coynes, Nizar Daboul, Kenneth Deck, Cyrus Desouza, Devasmita Dev, Monika Dhillon, Sohan Dua, Frank Eder, Mohamed El-Shahawy, John Ervin, Alberto Esquenazi, John Evans, Juan Frias, Claude Galphin, Adline Ghazi, Enrique Gonzalez, David Gorson, Barbara Greco, Rakesh Gulati, Jamal Hammoud, Kenneth Hershon, Daniel Hiser, George Hon, Claudia Hura, Aamir Jamal, Charles Kaupke, Elizabeth Kern, Rakhi Khanna, Zeid Khitan, Sun Kim, Nelson Kopyt, Csaba Kovesdy,

Gopal Krishna, Jeffrey (Jay) Kropp, Amrendra Kumar, Jayant Kumar, Mary Lawrence, John Lentz, Derek Lewis, Kenneth Liss, Hiralal Maheswari, Sreedhar Mandayam, Isam Marar, Bhasker Mehta, John Middleton, Jorge Mordujovich, Moustafa Moustafa, Samuel Mujica Trenche, Javier Narvarte, George Newman, Philip Nicol, Josier Nisnisan, A. Kaldun Nossuli, Andrew O'Shaughnessy, Chamberlain Obialo, Sarah Olelewe, Michael Oliver, John Padron, Rohit Pankhaniya, Devesh Patel, Gnyandev Patel, Humberto Pavon, Karlton Petteis, Walter Pharr, Andrea Phillips, Raman Punghalla, Luis Quesada-Suarez, Rajiv Ranjan, Sanjeev Rastogi, Jakkidi Reddy, Lisa Rich, Michael Robinson, Hector Rodriguez, Sylvia Rosas, Rallabhandi Sankaram, Ravi Sarin, Franklin Saumell, David Scott, Mohamed Sekkarie, John Sensenbrenner, Muhammad Shakeel, Michael Shanik, Sylvia Shaw, Stephen Smith, Richard Solomon, Amy Sprague, Pusadee Suchinda, Prasanth Surampudi, Sherry Sussman, Yaga Szlachcic, Michael Thompson, Fernando Trespalacios, Pilar Trueba, Marcel Twahirrwa, John Updegrove, Mark Vannorsdall, Freemu Varghese, Pedro Velasquez-Mieyer, Sailaja Ventrapragada, Khurram Wadud, Mark Warren, Ronald Watts, Daniel Weiner, Jean Welsh.

Supplementary Appendix 2. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

Diabetes-Related/Metabolic

1. History of diabetic ketoacidosis or type 1 diabetes mellitus (T1DM).

2. History of hereditary glucose-galactose malabsorption or primary renal glucosuria.

Renal/Cardiovascular

3. Known medical history or clinical evidence suggesting non-diabetic renal disease

4. Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant.

Note: Subjects with a history of treated childhood renal disease, without sequelae, may participate.

5. Uncontrolled hypertension (systolic blood pressure [BP] ≥180 and/or diastolic BP ≥100 mmHg) by Week –2.

Note: Subjects not fulfilling BP criteria at the initial screening visit may have their BP-lowering medication regimen adjusted, followed by re-evaluation up to the Week –2 run-in period (the angiotensin-converting enzyme inhibitor [ACEi] or angiotensin receptor blocker [ARB] regimen must be stable for at least 4 weeks before Day 1 to be eligible).

6. Blood potassium level >5.5 mmol/L during screening.

Note: Subjects in whom hyperkalaemia was associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs), β-blockers, or mineralocorticoid receptor antagonists (MRAs; eg, spironolactone or eplerenone), who have been withdrawn from these drugs, and in whom usage of these drugs is not indicated in the view of the treating physician, may be included in the study.

7. Myocardial infarction, unstable angina, revascularisation procedure (eg, stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before randomisation, or a revascularisation procedure is planned during the trial.

8. Current or history of heart failure of New York Heart Association (NYHA) class IV cardiac disease (The Criteria Committee of the NYHA).

9. Electrocardiogram (ECG) findings within 12 weeks before randomisation that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance).

Gastrointestinal

10. Known significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis).

Laboratory

11. Alanine aminotransferase (ALT) levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings are consistent with Gilbert's disease.

Other conditions

12. History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

13. History of human immunodeficiency virus (HIV) antibody positive.

14. Major surgery within 12 weeks before randomisation, or has not fully recovered from surgery.

15. Any condition that in the opinion of the investigator or sponsor's medical monitor would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified assessments.

16. History of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischaemia of the lower extremity within 6 months of screening (added 5 May 2016).

Medications/Therapies

17. Combination use of an ACEi and ARB.

18. Use of an MRA or a direct renin inhibitor (DRI).

Note: If deemed clinically appropriate at the discretion of the investigator, subjects may be removed from therapy with an MRA or DRI during screening. Subjects who are off therapy with an MRA or DRI for at least 8 weeks prior to randomisation may be considered eligible for enrolment.

19. Current use of a sodium glucose co-transporter 2 (SGLT2) inhibitor (within 12 weeks prior to randomisation).

20. Current participation in another canagliflozin study or previously exposed to canagliflozin in a prior canagliflozin study.

21. Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.

22. Received an active investigational drug (including vaccines) other than a placebo agent, or used an investigational medical device within 12 weeks before Day 1/baseline.

General

23. Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.

24. Employees of the investigator or study centre, with direct involvement in the proposed study or other studies under the direction of that investigator or study centre, as well as family members of the employees or the investigator.

Note: Investigators should ensure that all study enrolment criteria have been met and determine that the subject has not had any interval change in clinical status since the time of the initial screening visit. Before randomisation, subjects whose clinical status changes after screening such that they now meet an exclusion criterion should be excluded from participation.

Supplementary Appendix 3. Endpoint Criteria

End-stage kidney disease (ESKD)

In the absence of universally accepted guidelines that define the onset of ESKD, the following definitions have been developed to identify and adjudicate ESKD events.

1. Diagnosis

Worsening uraemia in patients progressing from chronic kidney disease (CKD) to ESKD causes characteristic symptoms which require renal replacement therapy (RRT) in the form of dialysis or transplantation. The requirement of ongoing RRT establishes the diagnosis of ESKD. In some cases, the diagnosis can be made in the absence of RRT when certain criteria are fulfilled.

- Kidney Transplantation: Definitive RRT prescribed when uraemic symptoms have already occurred, or are anticipated to occur, due to the progression of irreversible CKD. Death during the transplant surgery will be considered kidney transplantation.
- Chronic Dialysis: ESKD will be diagnosed if dialysis is performed for ≥30 days and is not subsequently known to recover. Indications for dialysis are indicated in Section 2 below.
- Dialysis Not Administered: In cases where dialysis is not available or not administered due to futility or subject refusal, the diagnosis of ESKD will require a sustained estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m^2 (by CKD Epidemiology Collaboration [CKD-EPI] formula and confirmed by repeat central laboratory measure at 30 days or more of the initial onset).

2. Onset of ESKD

The mode of onset of ESKD will be adjudicated into the following categories:

- Chronic progression.
- Acute deterioration, diagnosed when the decline in kidney function is sudden and acute kidney injury is superimposed on CKD, resulting in RRT.

3. Confirmation of ESKD

- In cases where RRT is given in the form of dialysis, the patient will be contacted at 90 days after the initiation of dialysis to document if dialysis is continuing.
- If the patient recovers renal function (defined as patient taken off dialysis because the physician evaluates that patient has enough renal function to live independently), the diagnosis of ESKD will be rescinded.
- If the patient is known to have received dialysis for >30 days but <90 days, and not known to recover, ESKD will be confirmed. The reason for the unavailability of information beyond 30 days should be clearly documented by the investigator.
- If dialysis was initiated, but not continued for 30 days due to death, futility of therapy, or transplantation, the patient will be considered to have reached ESKD. In this situation, the reason for discontinuation of dialysis should be clearly documented by the investigator.

4. Date of ESKD

- If an event is adjudicated as ESKD due to kidney transplantation, the date of the transplantation will be the date of the event if transplantation was the first form of RRT given.
- If an event is adjudicated as ESKD due to initiation of dialysis, the date when dialysis was initiated will be the date of the event.
- In cases where dialysis is unavailable, or not administered, the date of ESKD will be when eGFR falls below 15 mL/min/1.73 m^2. If a confirmatory central laboratory value cannot be collected due to death, and there is no evidence of acute kidney injury, the date of the event will be the date in which eGFR falls below 15 mL/min/1.73 m^2. If local and central laboratory tests are collected on the same day, the central laboratory value overrules the local laboratory value. Information around the presence or absence of symptoms of uraemia will also be collected for all patients meeting the ESKD endpoint; however, this will not affect the final adjudication decision, which will be based on the primary definition of ESKD as described in Sections 1 to 4 above.
- Symptomatic Uraemia: Symptomatic uraemia is diagnosed in the presence of the uraemic syndrome, which is a constellation of signs and symptom involving several different systems, including:
    - General: Pruritus, dry skin, fatigue, anhedonia;
    - Metabolic: Deterioration in nutritional status, recent significant weight loss, electrolyte or acid-base disturbances (severe hyperkalaemia or severe acidosis);
    - Gastrointestinal: Nausea, vomiting;

- Neurological: Neuropathy, encephalopathy, psychiatric disturbances, seizures;
- Volume overload, including difficult-to-control or accelerated hypertension;
- Bleeding diathesis not attributable to other causes;
- Pleuritis or pericarditis of uremic origin or other;
- Severe hyperparathyroidism.

- Advanced Asymptomatic Uraemia: The initiation of dialysis is generally performed when eGFR declines to <15 mL/min/1.73 m^2 on a subjective basis in anticipation of development of uraemic symptoms. If no symptoms are documented for initiation of dialysis, asymptomatic uraemia will be diagnosed. In the minority of patients who exhibit no symptoms even at very low eGFR values (such as <8 mL/min/1.73 m^2), however are initiated RRT in the view of benefits of therapy, the diagnosis will be of advanced asymptomatic uraemia.

Doubling of serum creatinine

Doubling of serum creatinine will be defined as a ≥2-fold increase in serum creatinine from the baseline assessment that persists for ≥30 days and is not thought to be due to reversible cause.

The baseline serum creatinine, as determined by averaging the 2 values closest to randomisation, will be used to compare subsequent values and determine if doubling of serum creatinine has occurred.

Both central serum creatinine values and local laboratory values may be used to calculate the increase in serum creatinine. The investigator will make all reasonable attempts to exclude reversible causes of elevation of serum creatinine such as volume depletion or nephrotoxic medication. The event will be adjudicated positively once the initial doubling of serum creatinine via local or central laboratory results has been confirmed by the central laboratory at ≥30 days, and if the process is determined to be irreversible.

If a confirmatory central laboratory value cannot be collected due to death or dialyses and there is no evidence of acute kidney injury, the event will be adjudicated positively.

The date of the event will be the date on which the creatinine first doubled. If central and local laboratory tests are collected on the same day, the central laboratory value overrules the local laboratory value.

Death

All deaths will be reviewed by the adjudicators to determine the cause of death, which will be classified as either renal death, cardiovascular (CV) death, or non-CV death.

Renal death

Renal death refers to deaths in patients who have reached ESKD who die prior to initiating RRT and no other cause of death is adjudicated. This may occur in the situations where either the patient refuses RRT or both the physician and the patient consider RRT futile and believe that

the patients' current quality of life, with their expected lifespan, outweighs the quality and quantity of life following RRT. This may also occur in situations where dialysis is not available. These events are classified as renal death when death occurs following refusal of dialysis AND no other cause of death is adjudicated. When a more specific cause of death is adjudicated, such as sepsis or trauma, the more specific cause will be designated as the primary cause of death.

CV death

CV death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to CV procedures, death due to CV haemorrhage, and death due to other CV causes.

1. Death due to Acute MI refers to a death by any CV mechanism (eg, arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days after an MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. We note that there may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤30 days of the MI, it will be considered a death due to MI.

   Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat an MI (percutaneous coronary intervention

[PCI], coronary artery bypass graft surgery [CABG]), or to treat a complication resulting from MI, should also be considered death due to acute MI.

Death resulting from an elective coronary procedure to treat myocardial ischaemia (ie, chronic stable angina) or death due to an MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. Sudden Cardiac Death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

   - Death witnessed and occurring without new or worsening symptoms
   - Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
   - Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
   - Death after unsuccessful resuscitation from cardiac arrest
   - Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac aetiology
   - Unwitnessed death in a subject seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-CV cause of death

(information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

Unless additional information suggests an alternate specific cause of death (eg, Death due to Other CV Causes), if a patient is seen alive ≤24 hours of being found dead, sudden cardiac death should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (eg, a subject found dead in bed, but who had not been seen by family for several days).

3. Death due to HF refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF aetiology. Deaths due to HF can have various aetiologies, including single or recurrent MI, ischaemic or non-ischaemic cardiomyopathy, hypertension, or valvular disease.

4. Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

5. Death due to CV Procedures refers to death caused by the immediate complications of a cardiac procedure.

6. Death due to CV Haemorrhage refers to death related to haemorrhage such as a non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or haemorrhage causing cardiac tamponade.

7. Death due to Other CV Causes refers to a CV death not included in the above categories but with a specific, known cause (eg, pulmonary embolism or peripheral arterial disease).

Definition of Non-CV Death

Non-CV death is defined as any death that is not thought to be due to a CV cause. The following is a suggested list of non-CV causes of death:

- Pulmonary
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (eg, systemic inflammatory response syndrome [SIRS])
- Haemorrhage that is neither CV bleeding nor a stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose

- Prescription drug reaction or overdose
- Neurological (non-CV)
- Malignancy
- Other non-CV, specify:

Definition of Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (eg, the only available information is “patient died”) or when there is insufficient supporting information or detail to assign the cause of death. This category of death should be avoided as much as possible and should only apply to a minimal number of patients.

Supplementary Appendix 4. CREDENCE Collaborative Network

Entity	Duties/responsibilities
Steering committee	• Responsible for the general and scientific oversight of the study, protocol development, study conduct, analysis of results and reporting. The SC includes leading scientific experts, as well as representatives of the Sponsor (non-voting) and the Academic Research Organization
Study sponsor	• Coordinates and collaborates with other relevant entities for the general scientific and operational oversight of the study • Fulfills country-specific regulatory requirements, including safety reporting requirements; registers and/or discloses the existence of and the results of the study as required by law • Provides funding for the study
Academic research organization (George Institute for Global Health)	• Provides oversight of the endpoint adjudication process in conduction with the Endpoint Adjudication Committee and Sponsor
Clinical research organization (Quintiles)	• Responsible for operations of the study, including site identification, investigator training, monitoring visits, data management, document translations, central IRB submissions, and other study logistics

Sponsor Medical Safety Review Committee	• Monitors patient safety by reviewing blinded data on a regular basis and refers safety concerns to an independent data monitoring committee (IDMC)
Independent data monitoring committee (IDMC)	• Reviews accumulated, unblinded safety information during the study and evaluates unblinded safety and efficacy results from a pre-specified interim analysis
Endpoint adjudication committee (EAC)	• Provides independent, external verification and confirmation of endpoints identified in the CREDENCE protocol in a blinded manner (ie, end-stage kidney disease, doubling of serum creatinine, death, myocardial infarction, stroke, hospitalized unstable angina, hospitalized congestive heart failure)
Biostatisticians	• Statistical analysis will be done independently and in parallel by the sponsor and also by the academic research organization according to details provided in the Statistical Analysis Plan
Study sites/investigators	• Responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements
Central laboratory	• Perform routine laboratory assessments in a standardized

	fashion according to the protocol's Time and Events Schedule • Provides confirmation of all laboratory-based study endpoints (eg, serum creatinine and eGFR)